AMENDMENTS TO THE DRAWINGS

The drawing sheet submitted herewith includes changes to the figure. This sheet replaces the original drawing sheet.

Appendix: Replacement sheet (1 sheet, 1 figure)

REMARKS

Status of the Claims

Claims 1-12, 14-21, 23 and 24 are currently pending in this application.

In this Response, claim 1 has been amended to address the Office's §112 concerns. No new matter has been added. Entry of the amendment and reconsideration on the merits in view of the following comments are respectfully requested.

Objection to the Drawing

A replacement drawing in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) is required. Specifically, the lettering and numbers contained in the drawing are corrected so as to be of proper size, uniform density, and well-defined (at least 1/8 inch or .32 cm in height) in compliance with 37 CFR 1.84(l) and (p)(1)-(5). The enclosed replacement drawing corrects these informalities.

The undersigned hereby states that no new matter has been added. Favorable consideration of the enclosed drawing is respectfully requested. Please substitute the enclosed drawing for the previously submitted drawing.

Rejections under 35 USC § 112, First Paragraph

Enablement

Claims 1-12, 14-21, 23 and 24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office has construed the limitation "90 minutes or less" as "encompassing time periods of virtually instantaneous processing, hybridization and detection." The Office asserted that "[a] review of the art fails to identify where such a method, or even the hybridization step alone, is completed instantaneously."

Applicants have amended claim 1 to delete the time limitation, thereby rendering this rejection moot. Accordingly, it is respectfully requested that this rejection be withdrawn.

Written Description

Claims 1-12, 14-21, 23 and 24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. As noted above, the Office construed the limitation "90 minutes or less" as "encompassing time periods of virtually instantaneous processing, hybridization and detection." The Office asserted that "[a] review of the art fails to identify where such a method, or even the hybridization step alone, is completed instantaneously," and therefore "the aspect of performing the claimed method in an instantaneous manner is deemed to constitute new matter."

As noted above, claim 1 has been amended to delete the time limitation, thereby rendering this rejection moot. Accordingly, it is respectfully requested that this rejection be withdrawn.

Rejection under 35 USC § 112, Second Paragraph

Claims 1-12, 14-21 and 23-24 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office asserted that it is unclear if the limitation of claim 1 "can be completed in 90 minutes or less" is a part of the claimed invention.

As noted above, claim 1 has been amended to delete the time limitation, thereby rendering this rejection moot. Accordingly, it is respectfully requested that this rejection be withdrawn.

Rejection under 35 USC § 103

Claims 1-12, 14-21, 23 and 24 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over applicant's admissions. MPEP § 2129. The Office quoted a number of statements from the specification and from the Response filed on September 2, 2009 pertaining to various aspects of the claimed method and concluded that "[i]n view of the admission by applicant that the method of lysing, hybridization, conditions that affect hybridization, probe synthesis, labeling and detection are all well known in the art, the claimed method is deemed to have been obvious to one of ordinary skill in the art at the time of applicant's invention." The Office further

cited *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955) for the proposition that "to the degree that argument has been presented that the claimed method is an optimization over prior-art methods, it is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. Applicants respectfully traverse this rejection.

The law of obviousness requires that the totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). "Known disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966). Moreover, omission of an element and retention of its function is an indicia of unobviousness. MPEP § 2144.04.II.B (*citing In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966), emphasis in original).

As Applicants pointed out in the previous Response, the present invention relates to new methods of improving the speed and efficiency of bacterial detection by eliminating the nucleic acid purification step prior to hybridization on a diagnostic microarray. It is not at all about "routine optimization" of "optimum or workable ranges" as was the case in *In re Aller, Lacey, and Hall*. Instead, it is about the omission of the entire step of nucleic acid purification, which was considered important at the time of the invention, while retaining the function of nucleic acid hybridization.

As the Office is well aware, the priority date of the present application is August 27, 2003. As of that date, a number of laboratories had reported the use of microarrays targeted to ribosomal RNA sequences (e.g., 16S rRNA) to differentiate between microbial species. However, RNA extraction from bacteria was required in all of those studies. Importantly, one of the bottlenecks in the use of microarrays for nucleic acid analyses was sample preparation. The claimed method using bacterial lysate without any nucleic acid purification or amplification steps is advantageous for the detection of clinical samples and for integration into automated systems for rapid identification of the pathogens. In order to show the state of the art at the time of the invention, passages from a number relevant prior art publications are reproduced below.

> "DNA microchip technology advantageously combines a rapid, high-throughput platform for nucleic acid hybridization with low cost and the potential for automation, although sample preparation procedures, including DNA and RNA isolation, fragmentation, and labeling, are still limiting steps."

(Bavykin *et al.*, "Portable system for microbial sample preparation and oligonucleotide microarray analysis," *Appl. Environ. Microbiol.* 2001, 67(2):922-928, at page 922, left column, emphasis added; attached hereto as ***Exhibit A***).

> "[U]se of microarrays and gene detection methods (in general) in many environmental applications is limited by (i) the time and labor required for manual sample handling, nucleic acid purification, and associated volume reduction, (ii) inefficient purification or concentration of nucleic acids at low target concentrations, especially in environmental samples, and (iii) the coextraction of inhibitory compounds that interfere with subsequent molecular manipulations, especially PCR."

(Small *et al.*, "Direct detection of 16S rRNA in soil extracts by using oligonucleotide microarrays," *Appl. Environ. Microbiol.* 2001, 67(10):4708-4716, at page 4708, left column, emphasis added; attached hereto as ***Exhibit B***; *see also* Chandler *et al.*, "Sequence versus structure for the direct detection of 16S rRNA on planar oligonucleotide microarrays," *Appl. Environ. Microbiol.* 2003, 69(5):2950-2958; attached hereto as ***Exhibit C***).

Additionally, Small *et al.* teach as follows:

> **Direct rRNA detection in amended soil extracts.** Successful hybridization and species-specific detection of intact rRNA (from a pool of total RNA) led us to investigate whether it was possible to directly detect rRNA in an unpurified soil extract with the microarray. Unpurified soil extracts and "clean" hybridization buffers were first seeded with decreasing amounts of *G. chapellei* or *D. desulfuricans* total RNA and then hybridized overnight at room temperature. For both RNA targets, the hybridization signal intensity was significantly reduced when a soil extract was present in the hybridization solution ($P < 0.05$) (Fig. 7). The array did not cross-hybridize to indigenous RNA in the soil extract (Fig. 7, 0 μg). The signal intensity from the biotinylated QC probe was unaffected by the presence of a soil extract, indicating that the soil extract was affecting RNA hybridization efficiency rather than enzymatic/fluorescent signal generation and subsequent image analysis. However, the signal intensity of the QC probes did vary from array to array and from day

> to day, illustrating the inherent variability in the analytical process (microarray fabrication, hybridization, detection). Regardless, adequate signal was produced with 0.5 μg of total RNA, representing approximately 7.5×10^6 cell equivalents of each species. For simple presence-or-absence determinations, detection of intact rRNA was as effective in a soil extract as it was in a clean hybridization buffer over the target concentration range reported here.

(Small *et al.* at page 4713, paragraph bridging left and right columns, and FIG. 7 on page 4714; emphasis added).

Thus, Small *et al.* teach hybridization between oligonucleotide probes printed on a planar substrate in a microarray format and purified rRNA that was spiked into an unpurified soil extract. It is important to note, however, that Small *et al.* do not teach hybridization between the oligonucleotide probes and indigenous rRNA from the unpurified soil extract, which could arguably be construed as reading on the pending claims. The Office must recognize that there is a significant distinction between previously purified rRNA that is manually mixed in with a crude bacterial lysate and rRNA that actually originates from the lysate. To the best of Applicants' knowledge, the present invention showed for the first time that successful hybridization could be accomplished between detection probes and/or oligonucleotide probes immobilized on a microarray and unpurified, unprocessed ribosomal RNA from a bacterial lysate.

As noted above, the predecessor of the Federal Circuit held that omission of an element and retention of its function is evidence of unobviousness. MPEP § 2144.04.II.B (*citing In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966)). The claims in *In re Edge* were directed to a printed sheet having a thin layer of erasable metal bonded directly to the sheet wherein said thin layer obscured the original print until removal by erasure. The prior art disclosed a similar printed sheet which further comprised an intermediate transparent and erasure-proof protecting layer which prevented erasure of the printing when the top layer was erased. The claims were found unobvious over the prior art because although the transparent layer of the prior art was eliminated, the function of the transparent layer was retained since appellant's metal layer could be erased without erasing the printed indicia. The Court stated that "[w]hile it may often be true that the mere omission of an

element together with its function does not produce a patentable invention, it may also be unobvious to omit an element while retaining its function" (citations omitted).

In this case, Applicants omitted RNA purification before hybridization with microarray probes, which was believed to be an important step at the time of the invention. Surprisingly, the function of hybridization was retained despite the lack of purification, and the presence of bacterial rRNA was successfully detected in a dose-dependent manner (*see* Example). As one can see from the results, the microarray was able to detect *S. aureus* rRNA from less than 1×10^6 bacterial cells (*see* the drawing and accompanying text at page 24, lines 1-12), which is about an order of magnitude less than the number of cells required to obtain a detectable signal in Small *et al.* (7.5×10^6, *see* quoted paragraph above).

In view of the foregoing, Applicants respectfully maintain that the claimed invention is nonobvious over the prior art and certainly nonobvious over Applicants own statements, as the Office asserted in the outstanding Office action. Accordingly, it is respectfully submitted that this rejection under 35 U.S.C. § 103(a) has been overcome and may properly be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 514572001600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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